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# Expiratory Flow Limitation in Elite Youth Cyclists

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Expiratory Flow Limitation in Elite Youth Cyclists

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## Abstract

Expiratory flow limitation (EFL) has been reported in pre-pubescent adolescents and elite, adult endurance athletes; however, the occurrence of EFL in elite adolescent endurance athletes has not been determined. **Purpose**: To determine incidence and severity of EFL in elite youth male cyclists of adolescent age. We hypothesized that elite, endurance trained youth will experience a higher prevalence and severity of EFL and dyspnea compared to an untrained control group. Pulmonary function will be similar pre- to post-exercise with bronchodilation occurring in both groups. **Methods**: 12 elite endurance- trained (ET) youth male cyclists (16.3 ± 1.0 years; 176.5 ± 6.2 cm; 64.2 ± 5.9 kg) and 12 recreationally active males (CON) (17.6 ± 2.2 years; 177.9 ± 7.1 cm; 74.8 ± 11.2 kg) completed an incremental test to exhaustion to determine peak oxygen consumption ($VO_{2peak}$) on a cycle ergometer. Heart rate and ventilation ($V_E$) were assessed throughout the exercise test. Dyspnea and ratings of perceived exertion (RPE) were assessed at the end of each stage. Subjects performed maximal flow volume loops (forced vital capacity (FVC), forced expiratory volume in 1-second ($FEV_1$), $FEV_1$/FVC, forced expiratory flow between 25-75% of FVC ($FEF_{25\text{-}75\%}$) and peak expiratory flow (PEF)) pre- and post- exercise. The occurrence and severity of EFL was quantified as the percentage of the expiratory tidal volume that overlapped with the maximum flow volume loop. **Results**: $VO_{2peak}$ in the ET group was 69.4±7.0 mL/kg/min and 45.7±3.9 ml/kg/min in the CON group. Peak power (390 ± 57 W vs. 273 ± 45 W) and peak $V_E$ (158 ± 18 L/min) were higher in ET vs. CON (124.7 ± 15.3). The ET group experienced significant EFL at $VO_{2peak}$ ($p < 0.001$), with 11/12 subjects exhibiting flow limitation. In the CON group, 5/12 subjects exhibited EFL. There was a significant change in pulmonary function from pre- to post-exercise in $FEV_1$ in both groups, with greater post-exercise bronchodilation in the CON group. There was no change in FVC, $FEV_1$/FVC, $FEF_{25-75\%}$ of FVC or PEF. The ET cyclists also had higher dyspnea ratings and RPE at peak exercise (8.5 ± 1.2, $p < 0.01$; 18.5 ± 1.2) than CON (6.3 ± 2.6, 17.2 ± 1.6).

**Conclusions**: Elite youth male cyclists have a higher occurrence of and severity of EFL at maximal exercise than recreationally active counterparts, which may limit exercise tolerance. Considering subjects are of pubertal age, or nearing the end of puberty, the participants may outgrow their flow limitation.

# Chapter I

## Expiratory Flow Limitation in Elite Youth Cyclists

*Introduction: Pulmonary System as a Limiting Factor to Exercise Tolerance*

The pulmonary system does not typically limit exercise tolerance in untrained, adult men when exercising at sea level (Dempsey et al. 1984); the arterial partial pressure of oxygen ($PO_2$) is maintained even during maximal exercise. Arterial $PO_2$ closely matches alveolar $PO_2$ since most people do not have a dramatic desaturation at maximal exercise; therefore, arterial $PO_2$ is used as a proxy for alveolar $PO_2$. There are some situations and population-specific exceptions, however, as pulmonary limitations have been reported in prepubescent children (Swain et al. 2010), women (Harms et al. 2006), the elderly (Johnson et al. 1994), diseased populations [(i.e. COPD patients (Pinto-Plata et al 2007)], and highly trained athletes (Mota et al 1999).

The partial pressure of arterial carbon dioxide ($P_aCO_2$) is regulated by increasing ventilation rates during exercise. Specifically, an increase in tidal volume and breathing frequency contribute to ventilation and regulation of $P_aCO_2$. Tidal volume (TV) is the first component to increase for higher ventilatory rates, due to the increases in end-inspiratory lung volume (EILV) and decreases in end-expiratory lung volume (EELV) (Aliverti 2008). TV increases during heavy exercise until it plateau's between 50-60% of vital capacity. Any increase in ventilation following that plateau comes from an increase in breathing frequency (BF) (Sheel et al. 2008). Under most conditions this increase in ventilation can be facilitated by the pulmonary system even during maximal exercise given the large ventilatory reserve (Aliverti 2008). However, expiratory flow limitation (constrained ventilation) may occur when the TV approaches and intersects the expiratory portion of the maximal-flow volume loop (Johnson et al. 1999). The expiratory flow limitation (EFL) and the connected hyperinflation of the lungs that occurs to avoid the expiratory portion of the maximal flow-volume loop presents a notable limitation in the pulmonary system, ultimately decreasing exercise tolerance by increasing dyspnea, exercise induced arterial hypoxemia (EIAH), and RMF (Babb et al. 1991). Dynamic hyperinflation increases inspiratory muscle work and may subsequently impair the function of inspiratory muscles (Mota 1999). The reduced dynamic lung compliance then causes an increased work of breathing which can ultimately limit exercise performance (McKenzie 2018). This inability to increase ventilation is associated with exercise-induced arterial hypoxemia (EIAH) (Johnson 1992), which will be discussed later.

EFL is caused by morphological limitations and can be exacerbated by differences in chemoreceptor sensitivity. The chemoreceptors sense changes in $O_2$ and $CO_2$ in the blood returning from limb locomotor muscles during exercise (Dempsey 2014). However, EFL also occurs due to the structural limitations of the lungs and airways, in which they can no longer keep up with the demands of exercise. The lungs and airways reach a limit where they cannot inflate any more than they already are, therefore, the individual’s anatomy limits the ability of the lungs to generate higher flow (Harms and Rosenkranz 2006).

Therefore, EFL can be explained by both the inability of the lungs and airways to meet the ventilatory demands of exercise, as well as the lack of responsiveness in generating higher flow rates due to reduced chemoreceptor sensitivity. As a result, maximal ventilation during exercise is limited by EFL (Mota 1999). When EFL occurs, subsequent consequences such as dyspnea, RMF, EIAH may also occur.

*Dyspnea*

Dyspnea is defined as uncomfortable sensations while breathing (American Thoracic Society). At maximal exercise, severe dyspnea occurs and decreases an individual's exercise tolerance (Weavil 2002). Weavil et al. found that when an individual experiences high levels of EFL during exercise, dynamic hyperinflation (DH) occurs and its implication is a feeling of breathlessness that can impair exercise tolerance. Interestingly, when flow limitation was imposed with a Starling resistor, severe dyspnea was experienced along with a 65% decrement in exercise performance, compared to the control trial without flow limitation and no dyspneic sensation (Iandelli 2002). While initial studies thought there was a strong connection between dyspnea and DH occurrence, recent studies have shown that dyspnea and exercise intolerance is actually associated more with EILV increases during exercise than DH (Calligaro; Guenette 2012).

*Dynamic Hyperinflation and Respiratory Muscle Fatigue*

When EELV increases above FRC and EILV increases near total lung capacity (TLC), it is termed dynamic hyperinflation (Johnson et al. 1999). EFL-induced DH has several consequences that can ultimately limit exercise tolerance. These consequences include dyspnea, RMF, constrained ventilation and gas exchange impairments. EFL may also cause EIAH to occur, especially in women who are more likely to experience EFL (Walls et al. 2002). EFL can cause inadequate hyperventilation and other altered breathing patterns that can increase the $O_2$ cost of breathing and work of breathing (Sheel et al. 2008). When DH occurs, expiratory work increases, resulting in airway closure that contributed to decreases in expiratory flow (Mota et al. 1999). DH has also been associated with dyspnea and impaired exercise tolerance (Pellegrino et al. 1993). While DH has been well-studied as a severe consequence of EFL, there is conflicting data regarding whether DH is the main factor limiting exercise tolerance. For example, Iandelli et al found that DH did not lead to impaired exercise tolerance in two of their six subjects when EFL was externally applied. DH did not contribute to dyspnea in their other four subjects until they achieved the highest severity of EFL in the exercise bout leading to their conclusion that DH may be overemphasized by some researchers in its role with exercise tolerance (Iandelli et al. 2002). In addition to EFL leading to possible DH and dyspnea, DH can also contribute to respiratory fatigue.

During higher intensities of exercise the respiratory muscles are recruited to a greater extent. At an intensity of greater than 80% of $VO_{2max}$ for ~3-5 min, diaphragmatic fatigue may occur (Babcock et al. 1995). When diaphragmatic fatigue occurs, the inspiratory muscle metaboreflex is initiated to vasoconstrict blood from the working limb locomotor muscles to the diaphragm (Wetter et al. 1999). The respiratory muscles demand more blood flow to prevent respiratory muscle fatigue. Harms et al. estimated that 14-16% of cardiac output during maximal exercise is shunted to the respiratory muscles (Harms, 2000). Vogiatzis et al found that the inspiratory muscle metaboreflex is initiated between 60-80% of maximal intensity exercise and then plateaued; blood flow to the respiratory muscles dropped off at maximal intensity exercise. They concluded that the demands of exercise placed on the respiratory system and working skeletal muscle could not be supported by the cardiovascular system at maximal exercise (Vogiatzis

2009). This shift in blood can limit exercise performance due to the skeletal muscle receiving less blood compared to the respiratory muscles (Aliverti 2008). Likewise, Harms et al. concluded that respiratory muscles can impact exercise tolerance when the workload is strenuous due to blood flow being redirected from the locomotor muscles to the respiratory muscles (Harms 2000). Regarding exercise intensity, Smith et al. reported that significant respiratory muscle fatigue occurred at 85% of $VO_{2max}$, but not at 70% of $VO_{2max}$ (Smith et al. 2014). This finding suggests that when athletes perform high intensity exercise the inspiratory muscle metaboreflex is initiated, which may lead to respiratory muscle fatigue. As mentioned previously, when EFL and DH are present, the oxygen cost of breathing increases (Johnson et al. 1999). The additional oxygen cost of breathing that results from DH can exacerbate exercise intolerance that was caused by pre-existing respiratory muscle fatigue and the inspiratory muscle metaboreflex.

*Special Populations*

Previous research has shown that EFL tends to affect specific populations. Prepubescent children in the United States have a high prevalence of EFL and EIAH. Children experience EFL due to their smaller lungs that are still developing, dysynaptic growth between the lungs and airways, and because their ventilation is higher at any given metabolic rate (Robben et al. 2013). Children have higher chemoreceptor sensitivity and regulate $CO_2$ at lower levels than adults. EFL is prevalent in 70-93% of untrained children (Emerson et al. 2015). In addition to the high prevalence of EFL among prepubescent children, aerobic training performed by prepubescent children may lead to greater ventilatory constraints (Nourry et al. 2005). However, the only longitudinal study, to our knowledge, reported that once prepubescent children reach puberty the prevalence of EFL decreases (Emerson et al. 2015). Emerson and colleagues state that this is most likely due to the pulmonary system further developing with maturation (Emerson et al. 2015).

In addition to the high prevalence of EFL in children, women also have a higher prevalence of EFL compared to men (Johnson et al. 1993). This usually occurs because of mechanical constraints due to differences in lung size, which limit the overall function of the pulmonary system. Also, women have less alveoli due to their smaller lungs which decreases the total surface area for diffusion (Mead, 1980). Women also have airway diameters that are smaller relative to their lung size compared to males leading to a lower dysynapsis ratio, which is associated with a greater prevalence of EFL (Mead, 1980). Women have a higher work of breathing compared to males due to a greater resistive work in the airways (Sheel et al. 2016). All of these limitations play a role in the presence and severity of EFL in women.

Patients with pulmonary disorders are also at risk for suffering from EFL. A study on patients with cystic fibrosis found that EFL presence in resting tidal volume could predict significant deterioration in lung function two years after its onset (Vilozni et al. 2016). The elderly population has also been shown to be affected by EFL due to the loss of elastic recoil of the lungs and airways with age, along with increased dead space at rest and during exercise (Turner et al. 1968, McKenzie, 2012).

Finally, elite adult athletes also display EFL. EFL occurs during severe intensity exercise in many highly trained endurance athletes and other subpopulations (Aliverti 2008, Mota et al. 1999, McKenzie 2012). Highly trained endurance athletes may intersect the boundary of their expiratory portion of the MFVL with their higher ventilation and become flow-limited (Aliverti 2008). While elite athletes have training adaptations to the cardiovascular and musculoskeletal systems, they do not have training adaptations to the pulmonary system in order to compensate for flow limitation (McKenzie 2012). The pulmonary system can be considered “underbuilt” compared to other systems due to its inability to adapt to training. Therefore during heavy intensity exercise, the mechanical constraints from the lungs size can limit the maximal inflation of their lungs, which training does not impact (Derchak 2000). Due to the increased metabolic and respiratory demand, the higher work of breathing during heavy exercise, concomitant hyperinflation, trained athletes often experience EFL which limits exercise tolerance (McKenzie 2012).

*Significance*

While EFL is present in the populations previously mentioned, the prevalence of EFL in elite, endurance-trained adolescents has yet to be addressed. Adolescents present a unique challenge due to their physiology. Previous studies have found that prepubescent children tend to “outgrow” their flow limitation once puberty is reached (Emerson 2015). Considering the prevalence of EFL is high in trained aerobic adult athletes, elite, adolescent cyclists are an interesting population. Throughout adolescence, the lungs and the airways may still be growing, and therefore the pulmonary system may pose a notable limitation. Therefore, the primary purpose of this study is to determine whether elite, endurance-trained adolescents experience EFL to a greater extent that age and lung-size matched counterparts. A secondary purpose is to examine whether subsequent consequences of EFL will be higher in the trained adolescents compared to their untrained counterparts. We predict that the elite, endurance-trained adolescents will experience EFL and its subsequent consequences to a greater extent and at a higher severity than their untrained peers.

In understanding the prevalence of EFL in elite adolescent cyclists compared to untrained age-matched non-endurance trained counterparts, we will gain a better understanding of how the pulmonary system contributes to impaired exercise tolerance in this unique demographic.

# Chapter II

## Methods

*Participants*

Twenty-four male subjects between the ages of 13 and 19 were recruited to participate in the study. The study was composed of an experimental group, consisting of elite, youth endurance-trained (ET) cyclists (n=12) and a control group (CON) of non-endurance trained, recreationally active subjects (n=12). The CON group were matched for age, height, and absolute lung size (e.g. forced vital capacity) with the ET group. All procedures were approved by the James Madison University Institutional Review Board and parental consent and youth assent was obtained prior to data collection.

*Experimental Design*

Following height, weight, and body composition measurements (Dual-energy X-Ray Absorptiometry (DEXA)), subjects performed maximal flow volume loops (MFVLs) on a SensorMedics 229 Metabolic Cart (SensorMedics Corp., Yorba Linda, Calif., USA). This pulmonary function test is the gold standard to assess the maximum capacity of the pulmonary system. Following the MFVL's, participants completed a maximal exercise test on a Velotron cycle ergometer (Velotron, Seattle, Washington, USA) until they reached volitional fatigue. At the end of each stage during the exercise test, inspiratory capacity (IC) maneuvers were performed. Immediately following the exercise test, the MFVLs were repeated.

*Body Composition*

Height was taken to the nearest 0.1 inch using a portable stadiometer (Invicta Height Measure; Invicta Plastics Limited, Leicester, England, UK) and weight was taken to the nearest 0.1 kg using a standard physician's scale (Pelouze 4040; Health o meter, Inc., Bridgeview, Illinois, USA). Next, the subject underwent a DEXA scan (Lunar iDXA, General Electric Company, Boston, Massachusetts, USA). For the DEXA scan, the subject laid supine for approximately 7-10 min until assessment of fat mass, fat free mass, and bone mineral density was completed.

*Pulmonary Function Measures*

All participants were given verbal prompts during these tests and were encouraged throughout the tests by the primary investigators. The subjects performed MFVLs pre- and post-exercise. All tests administered adhered to the ATS/ERS guidelines (Miller et al. 2005). Knudson (1983) reference values were used to calculate percent of predicted lung function. To achieve an acceptable MFVL, (1) the expiratory volume in $FEV_1$ must be <5% of the FVC or 0.150 L, whichever is greater; (2) there must be no cough during the first second of the expiratory portion; (3) the participant does not inhale too early (test does not terminate early); (4) there is no hesitation during the maneuver which may preclude an accurate measurement of $FEV_1$ and FVC; (5) there is no leak or obstruction in the mouthpiece and (6) the maneuver is performed correctly without an extra breath taken. In addition, the largest MFVL was used to assess EFL presence and severity. From the MFVL we obtained the values for forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC, peak expiratory flow (PEF), and forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$).

*Cardiopulmonary Exercise Testing*

A graded exercise test was performed until exhaustion to determine peak oxygen consumption ($VO_{2peak}$) on a Velotron cycle ergometer after the preliminary MFVL's.

Ratings of perceived exertion (RPE) and dyspnea were reported during each stage of the test. The ET group started at a self-selected wattage based on their previous training and the CON group started at 50 watts. The workload increased for both groups by 25 every 3 min until lactate threshold was reached. Lactate threshold was determined by finger sticks at the end of every 3-min stage using a Lactate Pro lactate analyzer (Arkray, Inc., Shiga, Japan). After lactate threshold was reached the subjects began the incremental protocol for the maximal exercise test at the wattage in the stage before lactate threshold was reached. In the incremental protocol, watts increased by 25 every min until volitional exhaustion was reached. At the end of each one-min stage subjects were asked to rate their dyspnea using the Dyspnea Numeric Rating Scale and RPE using Borg's 6-20 point scale. All subjects wore a PolarLink heart rate monitor (Bethpage, NY) throughout the entire test, and heart rate was recorded during the last 20 s of each stage. Ventilatory and metabolic data were recorded throughout the entire test.

*Expiratory Flow and Tidal Volume Assessment*

Tidal volume ($V_T$) was assessed through a bidirectional flow sensor during the $VO_{2peak}$ test. During the $VO_{2peak}$ test, inspiratory capacity (IC) maneuvers were performed during the last ~20 seconds of each one-min stage of exercise. The tidal flow-volume loops were placed inside the largest MFVL. We allowed for ~5 tidal volume loops to appear before the subject performs the IC maneuver to ensure end-expiratory lung volumes were consistent. The IC maneuvers were then placed within the post-exercise MFVL to assess EFL presence and severity. The subjects were given instruction on how to perform the IC maneuver and required to practice the maneuver at baseline before the $VO_{2peak}$ test was performed. EFL was determined by the percent of intersection of the tidal flow-volume loop with the expiratory portion of the MFVL by 5% of greater. A secondary investigator blinded to the initial calculations verified the percent of intersection initially measured by the primary investigator. If the measurements differed by >5%, a third investigator assessed the percent of the intersection and the closest two were averaged for analysis.

*Statistical Analysis*

Statistical analyses for this study was performed using SPSS v.24.0. All data was be checked for normality using the Shapiro-Wilk test to ensure parametric assumptions were met. Data was expressed as mean ± SD in tables and mean ± SE in figures. A 2x2 mixed ANOVA (time versus group) was used to determine differences pre- and post-exercise between the ET group and CON group. Significance was set to $p < 0.05$ for all analyses. Bonferroni adjustments were used to account for multiple comparisons. Pearson-product moment correlation coefficient was used to measure associations between severity of EFL and subsequent consequences.

# Chapter III

# Manuscript

**Expiratory flow limitation in elite youth cyclists.**

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## Abstract

Expiratory flow limitation (EFL) has been reported in pre-pubescent adolescents and elite, adult endurance athletes; however, the occurrence of EFL in elite adolescent endurance athletes has not been determined. **Purpose**: To determine incidence and severity of EFL in elite youth male cyclists of adolescent age. We hypothesized that elite, endurance trained youth will experience a higher prevalence and severity of EFL and dyspnea compared to an untrained control group. Pulmonary function will be similar pre- to post-exercise with bronchodilation occurring in both groups. **Methods**: 12 elite endurance- trained (ET) youth male cyclists (16.3±1.0 years; 176.5±6.2 cm; 64.2±5.9 kg) and 12 recreationally active males (CON) (17.6±2.2 years; 177.9±7.1 cm; 74.8±11.2 kg) completed an incremental test to exhaustion to determine peak oxygen consumption ($VO_{2peak}$) on a cycle ergometer. Heart rate and ventilation ($V_E$) were assessed throughout the exercise test. Dyspnea and ratings of perceived exertion (RPE) were assessed at the end of each stage. Subjects performed maximal flow volume loops (forced vital capacity (FVC), forced expiratory volume in 1-second ($FEV_1$), $FEV_1$/FVC, forced expiratory flow between 25-75% of FVC ($FEF_{25-75\%}$) and peak expiratory flow (PEF)) pre- and post-exercise. The occurrence and severity of EFL was quantified as the percentage of the expiratory tidal volume that overlapped with the maximum flow volume loop. **Results**: $VO_{2peak}$ in the ET group was 69.4±7.0 mL/kg/min and 45.7±3.9 ml/kg/min in the CON group. Peak power (390 ± 57 W vs. 273 ± 45 W) and peak $V_E$ (158 ± 18 L/min) we higher in ET vs. CON (124.7 ± 15.3). The ET group experienced significant EFL at $VO_{2peak}$ ($p < 0.001$), with 11/12 subjects exhibiting flow limitation. In the CON group, 5/12 subjects exhibited EFL. There was a significant change in pulmonary function from pre- to post-exercise in $FEV_1$ in both groups, with greater post-exercise bronchodilation in the CON group. There was no change in FVC, $FEV_1$/FVC, $FEF_{25-75\%}$ of FVC or PEF. The ET cyclists also had higher dyspnea ratings and RPE at peak exercise (8.5 ± 1.2, $p < 0.01$; 18.5 ± 1.2) than CON (6.3 ± 2.6, 17.2 ± 1.6). **Conclusions**: Elite youth male cyclists have a higher occurrence of and severity of EFL at maximal exercise than recreationally active counterparts, which may limit exercise tolerance. Considering subjects are of pubertal age, or nearing the end of puberty, the participants may outgrow their flow limitation.

The pulmonary system does not usually limit exercise tolerance in untrained, adult men when exercising at sea level (Dempsey et al. 1984). Under most conditions, the increase in ventilation can be maintained by the pulmonary system even during maximal exercise since there is large ventilatory reserve that can be utilized (Aliverti 2008). However, in specific populations, the pulmonary system may be a limitation during prolonged exercise and maximal exercise. Specifically, a condition called expiratory flow limitation (EFL; constrained ventilation) may occur in prepubescent children, women, elite adult endurance athletes, pulmonary disease patients, and the elderly, and it is characterized by a tidal volume ($V_T$) that approaches and intersects the expiratory portion of the maximal-flow volume loop (Johnson et al. 1999). The EFL and the associated hyperinflation of the lungs that occurs to avoid the expiratory portion of the maximal flow-volume loop presents a notable limitation in the pulmonary system, ultimately decreasing exercise tolerance (Babb et al. 1991).

In heavy endurance exercise, ventilatory requirements are extremely high to meet the metabolic demands of exercise. While this increase in metabolic demand is placed on the lungs, the total capacity of the lungs and chest wall to generate flow and increase volume does not adapt with exercise training, and therefore the total ventilatory capacity is not different between trained and untrained individuals.  In addition, several studies have suggested that highly trained individuals have altered chemoreceptor sensitivity and therefore lack and adequate hyperventilatory response to maximal exercise (Johnson 1992). Therefore, the lungs and airways reach a limit where they cannot inflate beyond their existing capacity, and this structural limitation precludes individuals from generating higher flow (Harms et al. 2006). With this morphological limitation, maximal ventilation during exercise is limited by EFL (Mota et al. 1999). In addition, the regulation of lung volumes [end-inspiratory lung volume (EILV) and end-expiratory lung volume (EELV)] also affects ventilatory constraint during exercise. When EELV increases above functional residual capacity (FRC) and EILV increases near total lung capacity (TLC), it is termed dynamic hyperinflation (DH) (Johnson et al. 1999). The presence of EFL and subsequent DH can limit exercise tolerance by increasing dyspneic sensations (Weavil et al. 2015), respiratory muscle fatigue (Dempsey et al. 2008) and gas exchange impairments (Weavil et al. 2015).

While EFL has been reported in specific populations, such as women (McClaran et al. 1998), older adults (Smith et al. 2017), pre-pubescent children (Swain et al. 2010, Smith et al. 2015), and endurance trained athletes (Johnson et al. 1992), the prevalence of EFL in elite, endurance-trained youth cyclists, has yet to be studied. Previous studies have found that prepubescent, recreationally active youth tend to "outgrow" their flow limitation once puberty is reached (Emerson et al. 2015). Still, while elite endurance athletes have training adaptations to the cardiovascular and musculoskeletal systems, their pulmonary system does not appear to adapt in a manner that can compensate for flow limitation (McKenzie, 2012). Considering the prevalence of EFL is high in aerobically trained adult athletes, elite youth cyclists of pubertal age are an interesting population to be studied. Moreover, given that the lungs and airways of youth endurance athletes may not have reached full development, yet the ventilatory and metabolic requirements are extremely high in heavy endurance exercise, the pulmonary system may pose a notable limitation to meet the demands of heavy exercise. Therefore, the primary purpose of this study was to determine the presence and severity of EFL in elite, endurance-trained (ET) youth cyclists of pubertal age compared to their age, height, and lung-size matched counterparts. The secondary purpose was to examine whether pulmonary function and dyspnea will be different during exercise in the ET group compared to an untrained control (CON) group. We predict that the ET youth cyclists will experience a higher prevalence and greater severity of EFL and dyspnea compared to CON group, however pulmonary function will be similar from pre- to post-exercise with bronchodilation occurring in both the ET and CON groups.

## Methods

*Participants*

Twenty-four male subjects between the ages of 13 and 19 were recruited to participate in the study. The study was composed of an experimental group, consisting of elite, endurance trained (ET) youth cyclists (n=12), and a CON group of non-endurance trained recreational cyclists (n=12). The CON group were matched for age, height, and absolute lung size (e.g. forced vital capacity) with the ET group. All procedures were approved by the James Madison University Institutional Review Board and parental consent and youth assent was obtained prior to data collection.

*Experimental Design*

Following height, weight, and body composition measurements [Dual-energy X-Ray Absorptiometry (DEXA)], subjects performed maximal flow volume loops (MFVL) on a SensorMedics 229 Metabolic Cart (SensorMedics Corp., Yorba Linda, Calif., USA). This pulmonary test is the gold standard to assess the maximum capacity of the pulmonary system. Following the MFVL's, participants completed a maximal exercise test on a Velotron cycle ergometer (Velotron, Seattle, Washington, USA) until they reached volitional fatigue (described below). At the end of each stage during the exercise test, inspiratory capacity (IC) maneuvers were performed. Immediately following volitional fatigue, the MFVLs were repeated.

*Anthropometrics*

Height was taken to the nearest 0.1 inch using a portable stadiometer (Invicta Height Measure; Invicta Plastics Limited, Leicester, England, UK) and weight was taken to the nearest 0.1 kg using a standard physician's scale (Pelouze 4040; Health o meter, Inc., Bridgeview, Illinois, USA). Next, the subject underwent a DEXA scan (Lunar iDXA, General Electric Company, Boston, Massachusetts, USA). For the DEXA scan, the subject laid supine for approximately 7-10 min until assessment of fat mass, fat free mass, and bone mineral density was completed.

*Pulmonary Function Measures*

All participants were given verbal prompts during this test and were encouraged throughout the test by the primary investigators. The subjects performed MFVLs pre- and immediately post-exercise. All of the pulmonary function tests that were administered adhered to the ATS/ERS guidelines (Miller 2005). Knudson (1983) reference values were used to calculate percent of predicted lung function. To achieve an acceptable maximum flow volume loop (MFVL): (1) the expiratory volume in FEV1 must be <5% of the FVC or 0.150 L, whichever is greater; (2) there must be no cough during the first second of the expiratory portion; (3) the participant does not inhale too early (test does not terminate early); (4) there is no hesitation during the maneuver which may preclude an accurate measurement of $FEV_1$ and FVC; (5) there is no leak or obstruction in the mouthpiece and (6) the maneuver is performed correctly without an extra breath taken. In addition, the largest MFVL was used to assess EFL presence and severity. From the MFVL we obtained the values for forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC, peak expiratory flow (PEF), and forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$).

*Cardiopulmonary Exercise Testing*

A graded exercise test was performed until exhaustion to determine $VO_{2peak}$ on a Velotron cycle ergometer after the MFVLs. Ratings of perceived exertion (RPE) and dyspnea were reported during each stage of the test. The ET group started at a self-selected wattage based on their previous training and the CON group started at 50 W. The workload increased for both groups by 25 W every 3-min until lactate threshold was reached. Lactate threshold was determined by finger sticks at the end of every 3-min stage using a Lactate Pro lactate analyzer (Arkray, Inc., Shiga, Japan). After lactate threshold was reached the subjects began the incremental protocol for the maximal exercise test at the wattage in the stage before lactate threshold was reached. In the incremental protocol, workload increased by 25 W every minute until volitional exhaustion was reached. At the end of each one-min stage subjects were asked to rate their dyspnea using the Dyspnea Numeric Rating Scale and RPE using Borg's 6-20 point scale. All subjects wore a PolarLink heart rate monitor (Bethpage, NY) throughout the entire test, and heart rate was recorded during the last 20 seconds of each stage. Ventilatory and metabolic data were recorded throughout the entire test.

*Expiratory Flow and Tidal Volume Assessment*

Tidal volume ($V_T$) was assessed through a bidirectional flow sensor during the $VO_{2peak}$ test. Prior to the $VO_{2peak}$ test, subjects were given instruction on how to perform the inspiratory capacity (IC) maneuver and were required to practice the maneuver at baseline. During the $VO_{2peak}$ test, IC maneuvers were performed during the last ~20 seconds of each one-min stage of exercise. We allowed for ~5 tidal volume loops to appear before the subject performed the IC maneuver to ensure end-expiratory lung volumes were consistent. The IC maneuvers were then superimposed within the post-exercise MFLV to assess EFL presence and severity. EFL was determined by the percent of intersection of the tidal flow-volume loop with the expiratory portion of the MFVL by

5% or greater. A secondary investigator blinded to the initial calculations verified the percent of intersection initially measured by the primary investigator. If the measurements differed by >5%, a third investigator assessed the percent of the intersection and the closest two were averaged for analysis. To assess EFL severity at specific exercise intensities, the $VO_2$ value that was closest to the correct intensity for each subject at 20%, 40%, 60%, 80% or 100% of $VO_{2peak}$, was used for the analysis. Assessing EFL severity over a relative range of values dependent on individual subjects responses during exercise has previously been used in the literature to measure EFL severity and operative lung volumes as a % of $VO_2$peak (Emerson et al. 2014, Guenette et al. 2010), or EFL severity and operative lung volumes over various ventilations (Smith et al 2017).

*Statistical Analysis*

Statistical analyses for this study were performed using SPSS v.24.0. All data was checked for normality using the Shapiro-Wilk test to ensure parametric assumptions were met. Data were expressed as mean ± SD in tables and mean ± SE in figures. A 2x2 mixed ANOVA (time versus group) was used to determine differences pre- and post-exercise between the ET group and CON group for EFL severity and changes in operating lung volumes. Significance was be set to $p < 0.05$ for all analyses. Bonferroni adjustments were used to account for multiple comparisons. Pearson-product moment correlation coefficient were used to measure associations between severity of EFL, ventilation and subsequent consequences (dyspnea and RPE).

## Results

*Subject Characteristics*

Subject characteristics are shown in Table 1. The ET group were matched to the CON group by age ($p$ = 0.085), height ($p$ = 0.616) and FVC ($p$ = 0.225). There was a significant difference between the two groups for weight ($p$ = 0.009) and body fat percentage ($p$ = 0.006). Maximal exercise and ventilatory values from the $VO_{2peak}$ test are shown in Table 2. At $VO_{2peak}$, the CON group had significantly lower absolute $VO_2$, relative $VO_2$, peak power, peak $V_E$ and $VCO_2$. Subjects in the CON group had significantly lower dyspneic ratings ($p$ = 0.014) and RPE ($p$ = 0.035) at peak exercise, but significantly higher RER values ($p$ = 0.001).

*Expiratory Flow Limitation*

EFL at 20, 40, 60, 80, and 100% of $VO_{2peak}$ is shown in Figure 1. Both ET and CON had significantly increased EFL severity from baseline to peak exercise ($p < 0.001$), however the ET group experienced a higher severity of EFL from baseline to peak exercise ($p$ = 0.001). Specifically, 11/12 subjects in the ET group were flow-limited and 5/12 in the CON group were flow limited, with 75.0 ± 32.9 % of EFL severity in the ET and 29.7 ± 40.4% of EFL severity in the CON group.

*Pulmonary Function*

Pulmonary function measurements are shown in Table 3. There were no significant differences in absolute lung volumes or flow rates between the ET and CON at baseline. From pre- to post-exercise, both groups significantly increased $FEV_1$ ($p$ = 0.002), $FEV_1$/FVC ($p < 0.001$), $FEF_{25\%-75\%}$ of FVC ($p < 0.001$), however there was no significant differences from pre- to post-exercise in FVC ($p$ = 0.096) or PEF ($p$ = 0.984). In addition, there was a significant interaction between the ET and CON groups over time in $FEV_1$ ($p = 0.025$), however not in FVC, $FEV_1$/FVC, $FEF_{25\%-75\%}$ of FVC, or PEF.

*Operating Lung Volumes*

Operating lung volumes (EILV and EELV) in CON and ET subjects are displayed in Figure 2 as a percentage of FVC. EELV decreased from baseline (36.5 ± 8.1% of FVC), at 20% (37.5 ± 9.7% of FVC) at 40% (34.9 ± 8.9% of FVC), 60% (34.8 ± 7.2% of FVC), 80% (34.7 ± 6.6% of FVC) and 100% of $VO_{2peak}$ (34.4 ± 7.8% of FVC), however changes were not significant as a main effect of time ($p = 0.219$) or between ET and CON across time ($p = 0.206$). There were significant increases in EILV across time points ($p < 0.001$) from baseline (59.8 ± 10.3% of FVC) to 100% of $VO_{2peak}$ (87.9 ± 7.9% of FVC), but no difference in EILV between the ET and CON groups across time ($p = 0.742$).

Ventilatory Responses to Exercise, EFL and Subsequent Outcomes

The present study found no associations between EFL and ventilation, dyspnea ratings, or RPE at $VO_{2peak}$ (Figures 3A-C). In addition, there was no association between the change in $FEV_1$ from pre- to post-exercise ($r = -0.025$, $p = 0.909$), or EFL with body fat percentage ($r = -0.217$, $p = 0.303$). Also, there was a significant increase in $V_E/VCO_2$ across time, however there was not a significant interaction between the ET and CON groups across time ($p = 0.895$). There was a significant increase in $V_E/VO_2$ throughout the exercise protocol ($p < 0.001$), however there was not a significant interaction between the ET and CON groups across time ($p = 0.314$).

## Discussion

*Major Findings*

This study investigated the prevalence and severity of EFL in elite, ET youth cyclists, in comparison to recreationally active untrained CON subjects matched by age, height, and lung-size (FVC). Our major finding was that the ET group had a greater EFL prevalence and severity than the CON group. In addition, post-exercise bronchodilation differed between the CON and ET groups, though it did not appear to be associated with EFL. Operating lung volumes were not different between the ET and CON groups, however EILV increased during exercise in both groups. Finally, though not associated with EFL severity, dyspnea ratings were higher in the ET group at peak exercise.

*EFL Presence and Severity in Trained vs Untrained Subjects*

There was a greater prevalence of EFL in the ET group, and a greater severity of EFL at peak exercise in the ET group compared to the CON group. While this is in agreement with the previous literature showing most (> 90%) endurance trained adult males have EFL (Johnson et al.), Emerson et al. conducted a longitudinal study that reported that untrained, adolescent subjects of similar age (15.3 ± 0.5 y) to the subjects in the present study (16.9 ± 1.8 y) tend to outgrow their flow-limitation. Specifically, Emerson et al. reported that 10 of 11 pre-pubertal boys exhibited EFL at $VO_{2max}$. Five years later, only 5 of these 11 subjects (measured post-pubertal) exhibited EFL at $VO_{2max}$.

In the present study, 11 out of 12 elite, ET cyclists exhibited EFL. These findings are consistent with several studies in endurance trained adult athletes, however the prevalence of EFL in endurance trained adult athletes is not consistent in the existing literature. Specifically, a study performed by Mota and colleagues showed that only 1 out of 10 competitive cyclists exhibited EFL at peak exercise. However, subjects in their study were 21 ± 5 years of age, and likely had reached full maturation. Therefore, discrepancies between the present study and Mota et al.'s work may be explained by maturation stage of the subjects. Yet differences may also exist due to the study methodology utilized for the assessment of EFL. Specifically, Mota et al. assessed endurance trained young adults by applying negative expiratory pressure at the mouth, where we used the overlap method that has been validated in many studies (Johnson et al. 1999, Smith et al. 2014, Chenoweth et al. 2015, Smith 2017). While both methods are acceptable and commonly used, not accounting for thoracic gas compression in the present study may overestimate the severity of EFL experienced (discussed in the limitations section) (Guenette et al. 2010). While differences exist in the study methodology, there are similarities in $VO_{2max}$ scores between subjects in both studies (72 ± 6 mL/kg/min in Mota and 69 ± 7 mL/kg/min in the present study) as well as similar ventilation at $VO_{2max}$ (147 ± 20 L/min and 157.5 ± 18.1 L/min, respectively). Taken together, these findings suggest that differences in reported EFL presence are due to either methodological differences and/or differences in lung size due to maturation stage, since age was different but not fitness level of the endurance athletes.

While Mota and colleagues suggest flow limitation is not prevalent in endurance trained athletes, several research studies report that EFL prevalence and severity is moderate-high in this unique population (Nourry et al. 2005, Johnson et al. 1992). Johnson and colleagues have found that 4/8 adult endurance runners exhibited EFL at peak exercise, yet another study reports most endurance trained cyclists exhibit EFL at peak exercise (> 80%) (Tecklenburg-Lund et al 2011). This difference in EFL presence could be partly due to the impact cycling posture has on operating lung-volumes in the riding position, which has recently been reported by Duke et al. (2014). However, the impact of different riding positions on EFL has yet to be determined in youth. While the literature reporting EFL presence is conflicting, it may be possible for endurance athletes to outgrow their flow limitation once they have reached full maturation. However, it is clear that not all individuals outgrow their flow limitation based on the prevalence of this phenomenon in highly fit adult athletes. Without a longitudinal study that follows the same cohort of endurance athletes from puberty into adulthood, we cannot determine whether these specific athletes will outgrow their flow limitation.

Interestingly, the only time point at which EFL severity was different between the CON and ET group was at peak exercise, which is supported by the existing literature where EFL has been reported in endurance trained adults. Specifically, Johnson and colleagues have shown that EFL does not appear until peak exercise, even when EFL was impending at moderate to heavy intensities. With impending EFL, DH occurs, and subjects breathe at a higher lung volume to meet the metabolic demands of heavy exercise. Johnson and colleagues reported that participants hyperventilated when breathing at higher lung volumes, exacerbating the mechanical constraint. Endurance trained athletes have an increased ventilatory requirement during exercise than non-trained counterparts due to higher achievable workloads, which leads to mechanical constraints at peak exercise (Johnson et al. 1992). In the present study, we matched the ET and CON group for height and FVC, and EFL was still present in both groups, but with a much greater percentage and severity at peak exercise in the ET group. Therefore, since FVC was matched in the ET and CON group, but absolute ventilation achieved was higher in the ET compared to the CON group, there is likely still an anatomical limitation present during pubertal age or immediately post-puberty, which subjects may outgrow into adulthood.

The present study found that there was no association between peak ventilation, dyspnea or RPE at peak exercise and severity of EFL. These findings are in agreement with that of Pianosi and colleagues (2019) who reported that youth and adolescent subjects exhibited EFL and dyspnea; however the degree of dyspnea was not associated with EFL or ventilation. Specifically, half of the subjects in their study cited difficulty breathing as their reason for stopping the exercise test. Several subjects that did not exhibit EFL still had dyspneic sensations that they cited as their primary reason for stopping the exercise test. In addition, dyspneic sensations have been reported to be higher when EFL is present, which may cause exercise intolerance (Stickland et al. 2012). Therefore, it is not surprising that the subjects in the ET group had higher dyspneic sensations compared to the CON group, but it was surprising that there were no associations between dyspnea and severity of EFL in the ET group.

*Pulmonary Function*

The only pulmonary function outcome measurements that were different from pre- to post-exercise were $FEF_{25\text{-}75\%}$, of FVC, $FEV_1$/FVC, and $FEV_1$. Interestingly, $FEV_1$ was the only variable from the PFTs to have a significant difference among the groups across time, showing there was a difference in bronchodilation from pre- to post-exercise in the CON group when compared to the ET group. $FEV_1$ typically increases post-exercise due to an increase in cartilage stiffness with increased ventilation rates during exercise. The difference in $FEV_1$ between the ET and CON groups over time is interesting because typically with higher ventilation rates, there is greater post-exercise bronchodilation. While bronchodilation occurs in normal, healthy airways, exercise-induced bronchoconstriction (EIB) occurs in approximately 10-50% of elite athletes depending on their sport and is especially common in athletes those who compete in national and international endurance events (Mohammadizadeh et al. 2013, Helenius et al. 1998). EIB is the narrowing of the large airways post-exercise and is caused by water loss from the airway membranes, which dries out the airways. Prolonged hyperventilation while training in conditions that expose endurance athletes to allergens and bronchial irritants during the exercise bout may increase EIB prevalence in an elite, endurance trained population (Helenius et al. 1998, 2000). Hyperventilation increases the pressure exerted on the airways and along with the lack of moisture, may cause damage to the airway's epithelium. This damage then triggers the injury-repair process which can lead to bronchial hyper-responsiveness, typically seen 5-15 min post-exercise, yet is resolved within an hour post-exercise (Kippelen et al. 2012, Rundell et al. 2002, McFadden et al. 1986). While EIB is typically reported in the 5-15 min post-exercise time period, bronchoconstriction has also been seen during exercise, which may impair exercise tolerance (Beck et al. 1994). In the present study, we only assessed pulmonary function pre- and post-exercise, and therefore it is difficult to determine whether the ET subjects were starting to exhibit or would have potentially had EIB. However, it is possible the individuals with the least amount of bronchodilation post-exercise could have had excessive drying of the airways, which is a cause of EIB, and this may have impacted exercise tolerance or post-exercise bronchodilation.

*Operating Lung Volumes and Ventilation*

An interesting finding in the present study was that there were no differences between groups in EELV across time-points, however there were increases in EILV, which is consistent with the previous literature. EILV increased steadily throughout the exercise test, similar to previous findings (Mota et al. 1999). In the present study, subjects that had flow limitation also showed DH, which explains the increase in EILV. Interestingly, the subjects in the CON group likely showed DH to avoid flow limitation, but may have reached volitional fatigue before having constrained ventilation due to EFL. Therefore, it is possible that with impending EFL, subject’s lungs began to hyperinflate, but ventilation did not need to reach high enough rates to be limited by their morphology. This may also explain why ventilation was not associated with EFL severity in flow-limited subjects (with CON and ET subjects combined). Whether DH occurs with impending EFL or when EFL first occurs still remains to be elucidated. The present findings for EELV are not in agreement with the majority of the current literature. Mota et al reported that EELV decreased during moderate intensity exercise by 13%, but then increased as they approached peak exercise due to DH, however their subjects exhibited EFL when DH occurred. Since the ET showed a high prevalence of EFL in the present study, the degree of DH was likely so high that significant changes in EELV were not present, even with much greater tidal volumes. In addition, the CON group experienced DH, but presumably did not achieve high enough workloads and ventilation rates to be flow-limited.

*Limitations*

The primary limitation of this project is that we did not account for thoracic gas compression, which may have led to an overestimation of EFL in our subjects. However, previous studies using independent measurements of transpulmonary pressures during expiration report a close agreement with the severity of EFL between methodologies (Johnson et al. 1991). Unfortunately, we were not able to obtain maturation status via Tanner Stages, and therefore were only able to match for age, FVC, and height. Due to their ages, it is likely that they are of nearing the end of puberty but are still considered youth. Also, this study also did not include female endurance athletes. Due to females having a higher prevalence of EFL and varying dysynapsis ratios (airway size relative to lung size), we cannot generalize our findings to the entire population of elite youth cyclists of both sexes. Finally, future studies should assess pulmonary function pre- and post-exercise, as well as 5, 10, and 30 min post-exercise to better understand airway function relative to ventilation rates and EFL severity.

*Future Directions*

Since the prevalence of EFL differs between the sexes, assessment of the prevalence and severity of EFL in an elite endurance trained female population should be conducted. Also, it would be interesting to elucidate the prevalence and severity of EIB in elite endurance youth of both sexes since the current data in adolescents is scarce. Perhaps the most interesting area for future research is to assess whether the ET cyclists in the current study outgrow their flow limitation, or remain flow limited into adulthood, which would provide important longitudinal data on the pulmonary system limitations to exercise throughout the lifespan.

*Conclusions*

This is the first study, to our knowledge, to investigate and identify a high prevalence of EFL in ET youth athletes of pubertal age or nearing the end of puberty.

Also, ET athletes have significantly greater EFL severity compared to recreationally active, untrained CON subjects matched for age, height and FVC. Whether or not these specific athletes will outgrow their flow limitation into adulthood is an interesting area for future research to better understand the development of the pulmonary system, as well as to understand possible limitations to exercise performance throughout the lifespan.

*Figure Legends*

Figure 1. Severity of EFL during exercise for the ET and CON groups. Severity of EFL across VO2 values (x-error bars included to represent ranges) for the ET (open circles) and CON (closed circles) groups. There was significantly greater EFL severity in both groups from baseline to VO2peak ($p<0.001$). Compared to the CON group, the ET group experienced an even greater severity of EFL at peak exercise ($p=0.004$). *Significantly different from CON group.

Figure 2. Operating lung volumes during exercise for ET and CON groups. Operating lung volumes across VO2 values (x-error bars included to represent ranges) for the ET (open circles) and CON (closed circles) groups. EELV did not change across time or between groups ($p>0.05$). EILV increased in both group ($p<0.05$), however was not different between the ET and CON groups. *Significantly different in ET and CON from baseline to VO2peak ($p<0.05$).

Figure 3a. Peak Ve as EFL severity in flow-limited subjects. There were 11 flow-limited subjects in the ET group and 5 subjects in the CON group).

Figure 3b. Dyspnea and EFL severity in flow-limited subjects.

Figure 3c. RPE and EFL severity in flow-limited subjects.

**Table 1. Subject characteristics of endurance trained athletes and recreationally active controls.**

| | ET (n = 12) | | | CON (n = 12) | | |
|---|---|---|---|---|---|---|
| | Mean | | SD | Mean | | SD |
| Age (years) | 16.3 | ± | 1.0 | 17.6 | ± | 2.2 |
| Height (cm) | 176.5 | ± | 6.2 | 177.9 | ± | 7.1 |
| Weight (kg) | 64.2 | ± | 5.9 | 74.8 | ± | 11.2* |
| Body mass index (BMI) ($kg/m^2$) | 17.1 | ± | 3.5 | 19.4 | ± | 4.0 |
| Body Fat (%) | 13.5 | ± | 2.8 | 18.4 | ± | 4.9* |

Values are mean ± SD.

*Significantly different between ET and CON ($p < 0.05$)

**Table 2. Maximal values in endurance trained athletes and recreationally active controls.**

| | ET (n=12) | | | CON (n=12) | | |
|---|---|---|---|---|---|---|
| | Mean | | SD | Mean | | SD |
| $VO_{2max}$ (ml/kg/min) | 69.4 | ± | 7.0 | 45.7 | ± | 3.9* |
| $VO_{2max}$ (L/min) | 4.5 | ± | 0.5 | 3.4 | ± | 0.4* |
| Peak Power (Watts) | 390.4 | ± | 56.8 | 273.0 | ± | 44.5* |
| Peak $V_E$ (BTPS) | 157.5 | ± | 18.1 | 124.7 | ± | 15.3* |
| $VCO_2$ (L/min) | 5.2 | ± | 0.6 | 4.3 | ± | 0.5* |
| Dyspnea | 8.5 | ± | 1.2 | 6.3 | ± | 2.6* |
| RPE | 18.5 | ± | 1.2 | 17.2 | ± | 1.6* |
| RER | 1.2 | ± | 0.1 | 1.3 | ± | 0.1* |
| $V_E/VO_2$ | 35.0 | ± | 3.2 | 37.0 | ± | 4.9 |
| $V_E/VCO_2$ | 30.2 | ± | 2.8 | 29.0 | ± | 2.3 |
| EELV (%FVC) | 35.8 | ± | 7.0 | 33.0 | ± | 8.5 |
| EILV (%FVC) | 87.9 | ± | 8.0 | 88.0 | ± | 0.9 |
| EFL | | 11/12 | | | 5/6 | |

Values are mean ± SD. $VO_2$, Oxygen consumption; $VCO_2$, carbon dioxide produced; $V_E$, ventilation; RPE, Rating of Perceived Exertion; RER, respiratory exchange ratio; $V_E/CO_2$, ventilatory equivalent for $VCO_2$; $V_E/VO_2$, ventilatory equivalent for $VO_2$; EELV, end expiratory lung volume; EILV, end inspiratory lung volume; EFL, expiratory flow limitation.

*Significantly different between ET and CON ($p < 0.05$)

**Table 3. Pulmonary function in endurance trained athletes and recreationally active controls.**

| | Pre-exercise | | Post-exercise | |
|---|---|---|---|---|
| | ET (n=12) | CON (n=12) | ET (n=12) | CON (n=12) |
| | Mean SD | Mean SD | Mean SD | Mean SD |
| Pulmonary Function (standard PFTs) | | | | |
| PEF (L/s) | 7.9 ± 2.0 | 7.9 ± 1.7 | 7.6 ± 1.4 | 8.3 ± 1.7 |
| FVC (L) | 5.1 ± 0.8 | 5.4 ± 0.8 | 5.0 ± 0.8 | 5.4 ± 0.8 |
| $FEV_1$ (L) | 4.1 ± 0.7 | 4.4 ± 0.9 | 4.1 ± 0.7[a] | 4.7 ± 1.0[a] |
| $FEV_1$/FVC | 80.2 ± 4.2 | 81.2 ± 6.3 | 83.7 ± 7.8[a] | 86.9 ± 6.8[a] |
| $FEF_{25-75\%}$ (L/s) | 3.9 ± 0.8 | 4.5 ± 1.5 | 4.3 ± 1.0[a] | 5.2 ± 1.6[a] |

Values are mean ± SD. PEF, peak expiratory flow; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; $FEV_1$/FVC, forced expiratory volume in 1 second/forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow at 25-75% of pulmonary volume.

[a] Significantly different between ET and CON from pre- to post-exercise ($p < 0.05$).

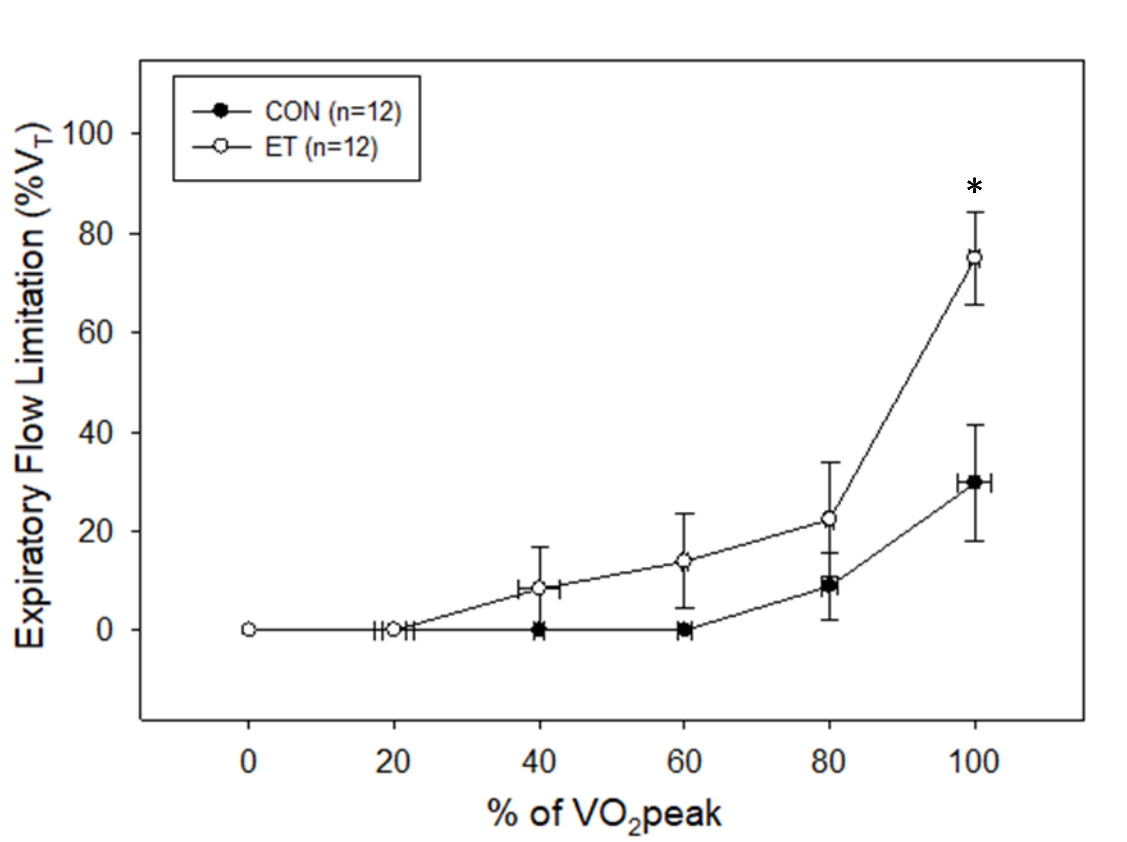



Figure 1. Severity of EFL during exercise for the ET and CON groups.

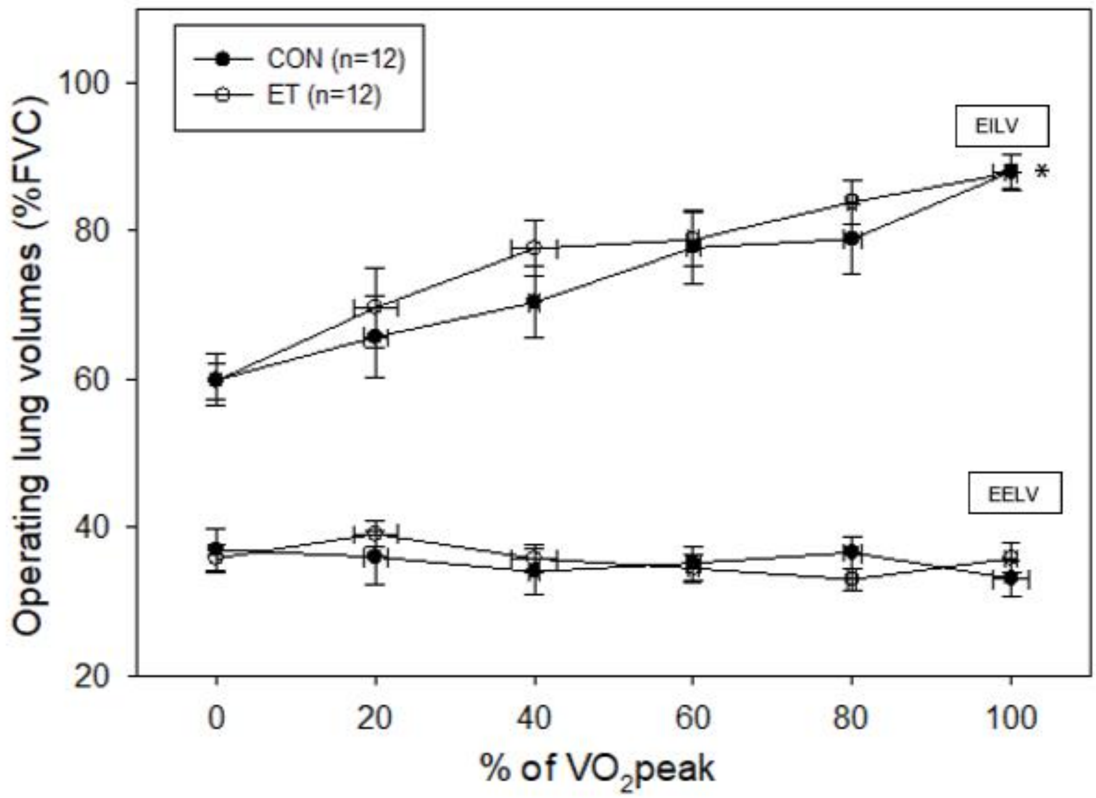



Figure 2. Operating lung volumes during exercise for ET and CON groups.

Figure 3a. Peak $V_E$ as EFL severity in flow-limited subjects. There were 11 flow-limited subjects in the ET group and 5 subjects in the CON group.

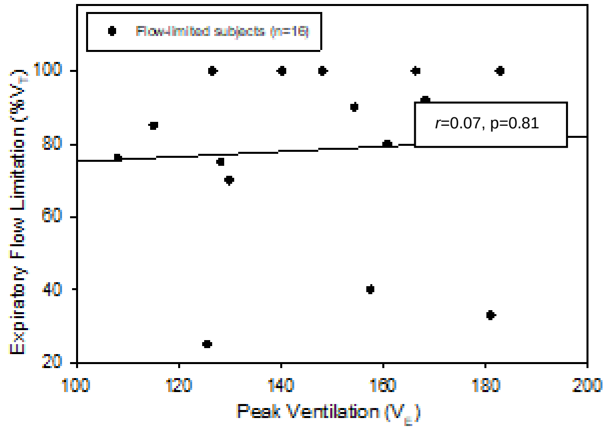



Figure 3b. Dyspnea and EFL severity in flow-limited subjects.

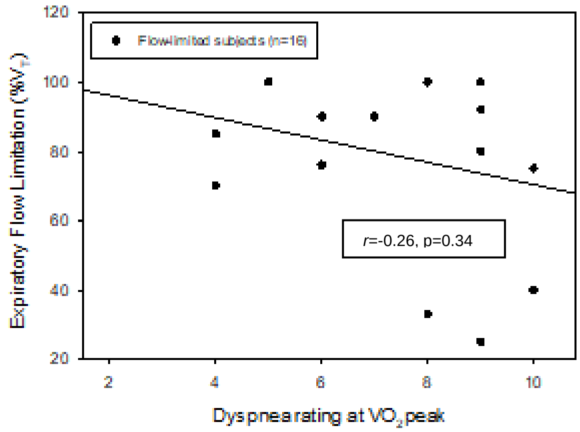
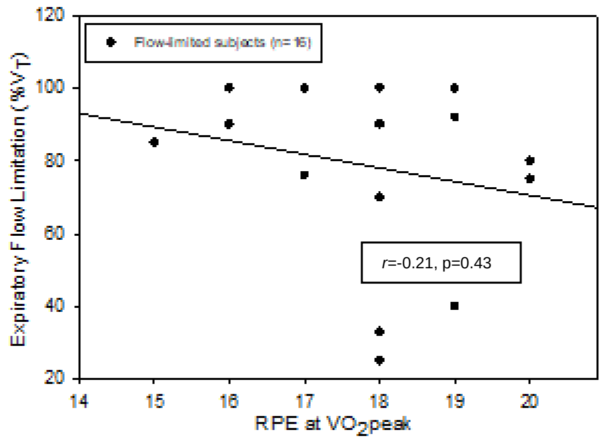



Figure 3c. RPE and EFL severity in flow-limited subjects.



**Respiratory responses to exercise and prevalence of expiratory flow limitation in adolescent endurance athletes and untrained controls.**

**Parent/Guardian Informed Consent**

**IRB #18-0548**

**Identification of Investigators & Purpose of Study**

Your child is being asked to participate in a research study conducted by Dr. Stephanie Kurti, Dr. Mike Saunders, Dr. Nick Luden, and Katherine Smith from James Madison University (JMU). The purpose of this study is to examine respiratory responses to exercise in endurance trained adolescent cyclists and recreationally active, untrained adolescent subjects.

**Research Procedures**

Should you decide to allow your child to participate in this research study, you will be asked to sign this consent form once all your questions have been answered to your satisfaction.

By participating in this study, the researchers will ask your child to perform (1) a body composition assessment, (2) a series of pulmonary function tests, (3) an exercise testing protocol and (4) a series of questionnaires. Each step is outlined in detail below. Additionally, to participate in the research, your child must be healthy and not diagnosed with any cardiovascular (i.e. heart murmur, aortic stenosis, unstable angina, active endocarditis, acute myocarditis, hypertension), pulmonary (i.e. obstructive or restrictive diseases), or metabolic diseases (i.e., type 1 and type 2 diabetes, insulin resistance, hyper/hypothyroidism); or any other diseases in these categories that are included in the American College of Sports Medicine guidelines.

1) Body composition assessment:
When your child first arrives to the laboratory, height, weight and body composition will be assessed. A DEXA analysis will be performed for body composition assessment. For the DEXA procedure, your child will be asked to lie down on their back and remain still for approximately 5-10 minutes until the scan is completed. All body composition assessment will be performed according to the American College of Sports Medicine guidelines.

2) Pulmonary Function Testing:
Following body composition assessment, your child will be asked to undergo standard pulmonary function testing according to the American Thoracic Society guidelines. Duration for the tests are dependent on the effort of your child and how quickly they learn to adequately perform the tests. Therefore, the duration of pulmonary function testing will be approximately 20-30 minutes total. These tests include nitrogen washout to assess total lung capacity (TLC). For this test, your child will simply breathe into a mouthpiece attached to the metabolic cart for ~7 minutes with a nose-clip on. After this, your child will perform the maximum flow-volume loop, where your child will be asked to perform a maximal inhale followed by a exhale where they will be asked to completely

empty their lungs and hold it for 6 seconds, followed by another maximum inhale. Next, your child will be asked to perform a maximal exhale, maximal inhale and then be asked to hold their breath for approximately 5 seconds, and then asked to perform another exhale. This test measures the diffusion capacity of the lung. The next respiratory test will be a test in which your child will maximally exhale and inhale against a closed valve to measure maximum inspiratory and expiratory pressures. Every pulmonary function test is non-invasive and only involves various breathing maneuvers.

3) Exercise Testing:
Your child will then perform an incremental exercise test until volitional fatigue. The exercise testing protocol will take approximately 15-20 minutes from start to complete. This test simply requires your child to start pedaling a bike at 50 watts (if recreationally active) or self-selected watts (if endurance trained in cycling) and increase the watts by 25 every 3 minutes until lactate threshold is reached. For lactate threshold, your child will undergo a finger stick at the end of every three-minute stages (typically three in total). When a specific blood lactate is reached, your child will undergo 1 minute stages increasing 25 watts/minute until volitional fatigue, or until they cannot turn the pedals anymore and choose to stop the test. Before and after the exercise test your child will complete several of the standard pulmonary function assessments described above.

**Time Required**

Participation in this study will require one session that will be approximately two hours in duration, in which all testing can be completed.

**Risks**

The investigators do not perceive more than minimal risks from your child's involvement in this study (that is, no risks beyond the risks associated with everyday life). Any potential risks associated with the testing itself were outlined in the consent forms for performance testing.

Additionally, the DEXA scan entails a low dose of radiation equivalent to approximately one transatlantic flight (0.015 mSv= milliseievert). While there is no validated questionnaire to define extensive exposure, radiation exposure is cumulative (200 DEXA scans is equal to the cumulative exposure of living at sea level for a year (3 mSv)). DEXA scans carry minimal X-ray exposure. To minimize exposure, the DEXA scan will only be performed once.

**Benefits**

1) The exercise test to volitional fatigue is the best indicator of overall health. This is an important and useful value for you and your child to be aware of. Additionally, we will let you know how he/she compared to individuals of the same age.
2) The data obtained from this project will be used to better understand the responses of adolescent athletes to high-level endurance training. Therefore, athletes may be able to use the data from this study to make well-informed decisions regarding your child's future training.

3) This research study will give physiologists, clinicians and sports practitioners more information about lung function and limitations to exercise tolerance, which may lead to improved advice for youth athletes.

It should be noted that while these are foreseeable benefits of your child's participation in the study, they are not guaranteed.

**Payment for participation**

There is no payment for taking part in this study.

**Confidentiality**

The results of this research will be presented in classroom presentations, conferences and research journals. Your child will be identified in the research records by a code name or number. The researchers retain the right to use and publish non-identifiable data. When the results of this research are published or discussed in conferences, no information will be included that would reveal your child's identity. All data will be stored in a secure location accessible only to the researchers. All information that matches up individual respondents with their code number will be stored in a secure location separate from their data.

There is one exception to confidentiality we need to make you aware of. In certain research studies, it is our ethical responsibility to report situations of child abuse, child neglect, or any life-threatening situation to appropriate authorities. However, we are not seeking this type of information in our study nor will you be asked questions about these issues.

**Participation & Withdrawal**

Your child's participation is entirely voluntary. He/she is free to choose not to participate. Should you and your child choose to participate, he/she can withdraw at any time without consequences of any kind.

**Questions about the Study**

If you have questions or concerns during the time of your child's participation in this study, or after its completion or you would like to receive a copy of the final aggregate results of this study, please contact Dr. Stephanie Kurti at kurtisp@jmu.edu and (630) 205- 6363, Dr. Mike Saunders at saundemj@jmu.edu and (540) 568-8121, Dr. Nicholas Luden at ludennd@jmu.edu and (540) 568-4069.

For any questions about Your Rights as a Research Subject, please contact Dr. David Cockley:
Chair, Institutional Review Board, James Madison University, (540) 568-2834, cocklede@jmu.edu

**Giving of Consent**

I have read this consent form and I understand what is being requested of my child as a participant in this study. I freely consent for my child to participate. I have been given satisfactory answers to my questions. The investigator provided me with a copy of this form. I certify that I am at least 18 years of age.

| | |
|---|---|
| Name of Child (Signed) | Date |
| Name of Parent/Guardian (Printed) | Date |
| Name of Parent/Guardian (Signed) | Date |
| Name of Researcher (Signed) | Date |

**YOUTH ASSENT FORM** (Ages 13-17)

IRB #18-0548

**Respiratory responses to exercise and prevalence of expiratory flow limitation in adolescent endurance athletes and untrained controls.**

We are inviting you to participate in this study because you are either a recreationally active adolescent individual, or currently are an endurance trained adolescent cyclist. We are interested in studying how your lung and airways responds to exercise, and may possibly limit your exercise ability.

By participating in this study, the researchers will ask you to perform (1) a body composition assessment, (2) a series of pulmonary function tests, (3) an exercise testing protocol and (4) a series of questionnaires. Each step is outlined in detail below. Additionally, you are not allowed to participate in this research study if you have been diagnosed with any cardiovascular, respiratory, or metabolic diseases. We will ensure with your parents that you have not been diagnosed with any of these types of diseases.

1) Body composition assessment:
When you first arrive to the laboratory, height, weight and body composition will be assessed. An analysis will be formed for body composition assessment (fat mass and lean muscle mass). To minimize exposure, the scan will only be performed once. For the DEXA procedure, you will be asked to lie down on your back and remain still for approximately 5-10 minutes until the scan is completed. All body composition assessment will be performed according to the American College of Sports Medicine guidelines.

2) Pulmonary Function Assessment:
Following body composition assessment, you will be asked to undergo standard pulmonary function testing (to test how your lungs function) according to the American Thoracic Society guidelines. Tests are dependent on your effort and how quickly you learn to adequately perform the tests. Therefore, the duration of pulmonary function testing will be approximately 20-30 minutes total. These tests include a test where we can first measure the total capacity of your lungs. For this test, you will simply breathe into a mouthpiece attached to the metabolic cart for ~7 minutes with a nose-clip on. After this, you will perform a test where you will be asked to perform a maximal inhale followed by a exhale where you will be asked to completely empty your lungs and hold it for 6 seconds, followed by another maximum inhale. Next, you will be asked to perform a maximal exhale, maximal inhale and then be asked to hold your breath for approximately 5 seconds, and then asked to perform another exhale. This test measures the diffusion capacity of your lung. The next respiratory test will be a test in which you will maximally exhale and inhale against a closed valve to measure maximum inspiratory and expiratory pressures. Every pulmonary function test is non-invasive and only involves various breathing maneuvers.

3) Exercise Testing:

You will then perform an incremental exercise test until volitional fatigue. The test duration is only about 15-20 minutes from start to finish. This test simply requires you to start pedaling a bike at 50 watts (if recreationally active) or self-selected watts (if endurance trained in cycling) and increase the watts by 25 every 3 minutes until lactate threshold is reached. For lactate threshold, you will undergo a finger stick at the end of every three-minute stages (typically three in total). When a specific blood lactate is reached, you will undergo 1 minute stages increasing 25 watts/minute until volitional fatigue, or until you cannot turn the pedals anymore and choose to stop the test. Before and after the exercise test you will complete the standard pulmonary function assessment described above.

Your individual data will be completely confidential. No information will be revealed in presentations or publications of the data that will reveal your identity.

We have asked your parents for their permission for you to do this study. Please talk this over with them before you decide whether or not to participate by completing the performance testing and all questionnaires.

If you have any questions at any time, please ask one of the researchers.

If you check "yes," it means that you have decided to participate and have read everything that is on this form. You and your parents will be given a copy of this form to keep.

______ Yes, I would like to participate in the study.

_______________________________________ ________________

Signature of Subject Date

_______________________________________ ________________

Signature of Investigator Date

If you have any questions or concerns, please contact Dr. Stephanie Kurti at kurtisp@jmu.edu and (630) 205-6363, Dr. Mike Saunders at saundemj@jmu.edu at (540) 568-8121, Dr. Nicholas Luden at ludennd@jmu.edu and (540) 568-4069.

**Respiratory responses to exercise and prevalence of expiratory flow limitation in adolescent endurance athletes and untrained controls.**

**Informed Consent (18 years of age and older)**

**IRB #18-0548**

**Identification of Investigators & Purpose of Study**

You are being asked to participate in a research study conducted by Dr. Stephanie Kurti, Dr. Mike Saunders, Dr. Nick Luden, and Katherine Smith from James Madison University (JMU). The purpose of this study is to examine respiratory responses to exercise in endurance trained adolescent cyclists and recreationally active, untrained adolescent subjects. Additionally, to participate in the research, you must be healthy and not diagnosed with any cardiovascular (i.e. heart murmur, aortic stenosis, unstable angina, active endocarditis, acute myocarditis, hypertension), pulmonary (i.e. obstructive or restrictive diseases), or metabolic diseases (i.e., type 1 and type 2 diabetes, insulin resistance, hyper/hypothyroidism); or any other diseases in these categories that are included in the American College of Sports Medicine guidelines.

**Research Procedures**

Should you decide to participate in this research study, you will be asked to sign this consent form once all your questions have been answered to your satisfaction.

By participating in this study, the researchers will ask you to perform (1) a body composition assessment, (2) a series of pulmonary function tests, (3) an exercise testing protocol and (4) a series of questionnaires. Each step is outlined in detail below.

1) Body composition assessment:
When you first arrive to the laboratory, height, weight and body composition will be assessed. A DEXA analysis will be performed for body composition assessment. For the DEXA procedure, you will be asked to lie down on their back and remain still for approximately 5-10 minutes until the scan is completed. All body composition assessment will be performed according to the American College of Sports Medicine guidelines.

2) Pulmonary Function Testing:
Following body composition assessment, you will be asked to undergo standard pulmonary function testing according to the American Thoracic Society guidelines. Duration for the tests are dependent on you effort how quickly you learn to adequately perform the tests. Therefore, the duration of pulmonary function testing will be approximately 20-30 minutes total. These tests include nitrogen washout to assess total lung capacity (TLC). For this test, you will simply breathe into a mouthpiece attached to the metabolic cart for ~7 minutes with a nose-clip on. After this, you will perform the maximum flow-volume loop, where you will be asked to perform a maximal inhale followed by a exhale where you will be asked to completely empty their lungs and hold it for 6 seconds, followed by another maximum inhale. Next, you will be asked to perform

a maximal exhale, maximal inhale and then be asked to hold your breath for approximately 5 seconds, and then asked to perform another exhale. This test measures the diffusion capacity of the lung. The next respiratory test will be a test in which you will maximally exhale and inhale against a closed valve to measure maximum inspiratory and expiratory pressures. Every pulmonary function test is non-invasive and only involves various breathing maneuvers.

3) Exercise Testing:
You will then perform an incremental exercise test until volitional fatigue. The exercise testing protocol will take approximately 15-20 minutes from start to complete. This test simply requires you to start pedaling a bike at 50 watts (if recreationally active) or self-selected watts (if endurance trained in cycling) and increase the watts by 25 every 3 minutes until lactate threshold is reached. For lactate threshold, you will undergo a finger stick at the end of every three-minute stages (typically three in total). When a specific blood lactate is reached, you will undergo 1 minute stages increasing 25 watts/minute until volitional fatigue, or until you cannot turn the pedals anymore and choose to stop the test. Before and after the exercise test you will complete several of the standard pulmonary function assessments described above.

**Time Required**

Participation in this study will require one session that will be approximately two hours in duration, in which all testing can be completed.

**Risks**

The investigators do not perceive more than minimal risks from your involvement in this study (that is, no risks beyond the risks associated with everyday life). Any potential risks associated with the testing itself were outlined in the consent forms for performance testing.

Additionally, the DEXA scan entails a low dose of radiation equivalent to approximately one transatlantic flight (0.015 mSv= milliseievert). While there is no validated questionnaire to define extensive exposure, radiation exposure is cumulative (200 DEXA scans is equal to the cumulative exposure of living at sea level for a year (3 mSv)). DEXA scans carry minimal X-ray exposure. To minimize exposure, the DEXA scan will only be performed once.

**Benefits**

1) The exercise test to volitional fatigue is the best indicator of overall health. This is an important and useful value for you to be aware of. Additionally, we will let you know how you compared to individuals of the same age.
2) The data obtained from this project will be used to better understand the responses of adolescent athletes to high-level endurance training. Therefore, athletes may be able to use the data from this study to make well-informed decisions regarding your future training.

3) This research study will give physiologists, clinicians and sports practitioners more information about lung function and limitations to exercise tolerance, which may lead to improved advice for youth athletes.

**Payment for participation**

There is no payment for taking part in this study.

**Confidentiality**

The results of this research will be presented in classroom presentations, conferences and research journals. You will be identified in the research records by a code name or number. The researchers retain the right to use and publish non-identifiable data. When the results of this research are published or discussed in conferences, no information will be included that would reveal your identity. All data will be stored in a secure location accessible only to the researchers. All information that matches up individual respondents with their code number will be stored in a secure location separate from their data.

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**Participation & Withdrawal**

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**Questions about the Study**

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| | |
|---|---|
| Name of Participant (Signed) | Date |
| Name of Researcher (Signed) | Date |

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